Alef Medical Argentina

CONVUPIDIOL®

Pharmacovigilance Report #6

Long-Term Real-World Follow-Up of Convupidiol® (Purified Cannabidiol) in Patients with Drug-Resistant (Refractory) Epilepsy

Marketing Authorization Holder (MAH): Alef Medical Argentina S.A.

Data Cut-Off Date: February 27, 2026

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Alef Medical Argentina

Dear Healthcare Professional,

We are pleased to share the Sixth Pharmacovigilance Report for Convupidiol® (Purified Cannabidiol), providing essential real-world clinical data to support treatment optimization in your clinical practice.

This report reinforces Alef Medical's ongoing commitment to patient safety under the Risk Management Plan (RMP) approved by ANMAT, expanding the safety and efficacy profile of Convupidiol® through rigorous, confidential monitoring in full compliance with Personal Data Protection Law No. 25,326.

This update includes longitudinal follow-up of previously enrolled cohorts alongside newly incorporated patients. During this reporting period, 16 prescribing physicians contributed data from 206 patient consultations. To date, a cumulative total of 38 specialists have participated in this national registry, creating a robust longitudinal database.

Maintaining our established methodology, baseline seizure frequencies were recorded and re-evaluated at 6, 12, 12–24, 24–36, and >36 months of continuous treatment. Notably, data from patients with over 3 years (>36 months) of ongoing therapy offer invaluable insights into long-term efficacy and safety.

To ensure maximum objectivity and data integrity, all information was collected and independently audited by IPRAT S.A., a specialized pharmacovigilance Contract Research Organization (CRO). We trust these evidence-based findings will assist you in daily clinical decision-making.

We remain at your full disposal for any scientific queries. Your active participation remains essential to advancing real-world pharmacovigilance and optimizing patient care.

Dr. Diego Sarasola

Medical Director
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EXECUTIVE SUMMARY

Convupidiol® was the first plant-derived purified cannabidiol formulation approved as a pharmaceutical product by ANMAT (December 3, 2020). Comprehensive pharmacovigilance operations have been conducted in close collaboration with prescribing specialists to continuously monitor real-world outcomes.

Participating physicians registered patients in strict adherence to Personal Data Protection Law No. 25,326. Registry parameters included baseline seizure frequency and prospective follow-up assessments. Multiple reporting channels (dedicated registry forms, telephone lines, and secure digital platforms) were provided for adverse event (AE) reporting.

Upon receipt of an AE report, the Alef Medical Pharmacovigilance Department initiated systematic case processing, investigation, and follow-up. All reported adverse events were expedited or periodically submitted to ANMAT in accordance with regulatory mandates.

In compliance with Good Pharmacovigilance Practices (GVP) and data protection laws, all patient data are fully anonymized and kept strictly confidential.

Abbreviations:

ANMAT	National Administration of Drugs, Foods and Medical Devices
CBD	Cannabidiol
FVG	Pharmacovigilance
THC	Tetrahydrocannabinol

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1. INTRODUCTION

1.1 Product Description

Convupidiol® is a pharmaceutical-grade oral solution containing highly purified plant-derived cannabidiol (CBD).

The exact mechanisms underlying the anti-seizure effects of cannabidiol in humans are not fully elucidated. CBD does not exert its anticonvulsant activity via classical CB1 or CB2 cannabinoid receptors. Proposed mechanisms include reduction of neuronal hyperexcitability through antagonism of G protein-coupled receptor 55 (GPR55), desensitization of Transient Receptor Potential Vanilloid 1 (TRPV1) channels, and inhibition of adenosine reuptake via Equilibrium Nucleoside Transporter 1 (ENT-1). CBD lacks CB1 agonist activity and does not produce psychotropic effects.

Cannabidiol undergoes extensive hepatic metabolism primarily mediated by CYP3A4 and CYP2C19 enzymes. In vitro, CBD exhibits broad-spectrum inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP3A4 isoenzymes.

Cannabidiol was approved as an anti-seizure medication by the US FDA in 2018 (Epidiolex®). In Argentina, Convupidiol® received official regulatory approval from ANMAT on December 3, 2020 (Certificate No. 59,304).

1.2 Therapeutic Indications

Convupidiol® is indicated as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients aged 2 years and older, and for seizures associated with Tuberous Sclerosis Complex (TSC) in patients aged 1 year and older.

1.3 Recommended Posology & Titration Schedule

The recommended starting dose is 2.5 mg/kg twice daily (5 mg/kg/day). After 1 week, the dose should be increased to a target maintenance dose of 5 mg/kg twice daily (10 mg/kg/day).

Based on individual clinical response and tolerability, the dose may be titrated in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day) up to a maximum recommended maintenance dose of 10 mg/kg twice daily (20 mg/kg/day).

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In clinical scenarios where more rapid titration is warranted, dosage escalation from 10 mg/kg/day to 20 mg/kg/day may proceed in bi-daily increments.

1.4 Clinical Pharmacology & Mechanism of Action

Mechanism of action.

The precise mechanisms by which cannabidiol exerts its anticonvulsive effects in humans are unknown. Cannabidiol does not exert its anticonvulsive effect through interaction with the receptors of the cannabinoid. CBD attenuates neuronal hyperexcitability via intracellular calcium modulation through GPR55 receptor antagonism and TRPV1 channel regulation, alongside enhanced purinergic signaling via equilibrium nucleoside transporter 1 (ENT-1) inhibition.

Pharmacokinetic Drug Interactions.

A synergistic anti-seizure effect may occur due to bidirectional pharmacokinetic interactions between CBD and clobazam. Co-administration leads to elevated circulating plasma levels of their active metabolites: 7-OH-CBD (~1.5-fold increase) and N-desmethylclobazam (N-CLB, ~3-fold increase).

2. SAFETY PROFILE SUMMARY

2.1 Adverse Reactions

Summary of the security profile.

The most frequently reported adverse drug reactions include somnolence, decreased appetite, diarrhea, pyrexia, fatigue, and vomiting.

2.2 Regulatory Actions Taken for Safety Reasons

No regulatory or safety-related actions were taken during this reporting period. All routine Periodic Safety Update Reports (PSURs/PBRERs) were fulfilled in accordance with ANMAT regulatory mandates.

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3. REAL-WORLD PHARMACOVIGILANCE DATA

3.1 Cumulative Patient Exposure

This report covers the monitoring period from July 11, 2025, to February 27, 2026. Data collection maintained the confidential registry format completed by prescribing specialists. The primary objectives were longitudinal evaluation of seizure frequency and adverse event recording.

Baseline seizure frequency was recorded at treatment initiation, followed by prospective evaluations at 6, 12, 13–24, 24–36, and >36 months. Prescribers managed patients according to their routine clinical judgment.

During this reporting period, 16 specialists contributed follow-up data from 206 anonymized patient visits. Cumulatively, 38 specialists have contributed to the national registry program since inception.

3.2 Patient Consultation Distribution by Follow-Up Interval

As of the data cut-off date (February 27, 2026), 206 patient consultations were evaluated:

	# visits	**%**
6-Month Follow-Up	49	24%
12-Month Follow-Up	23	11%
13-24 Month Follow-Up	33	16%
24-36 Month Follow-Up	43	21%
36 Month Long-Term Follow-Up	56	27%
Incomplete/Invalid Data	2	1%
Total Evaluated Consultations	**206**	**100%**

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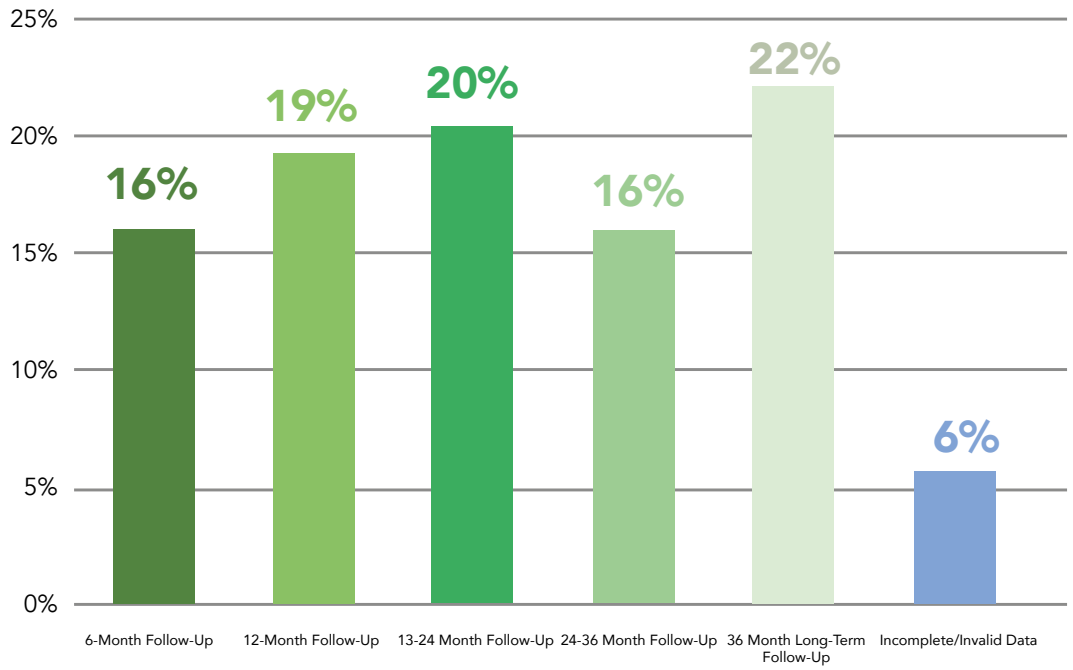
Visits of patients evaluated in the period Oct- 01-2024 to Jul -10-2025



3.3 Demographic Distribution by Age Groups

Patient age distribution across the evaluated cohort was balanced across pediatric and young adult groups:

Age range	# patients	%
<5 years	51	25%
6 - 10 years	63	31%
11 - 16 years	57	28%
>16 years	35	17%
Not reported	0	0%
Total	**206**	**100%**

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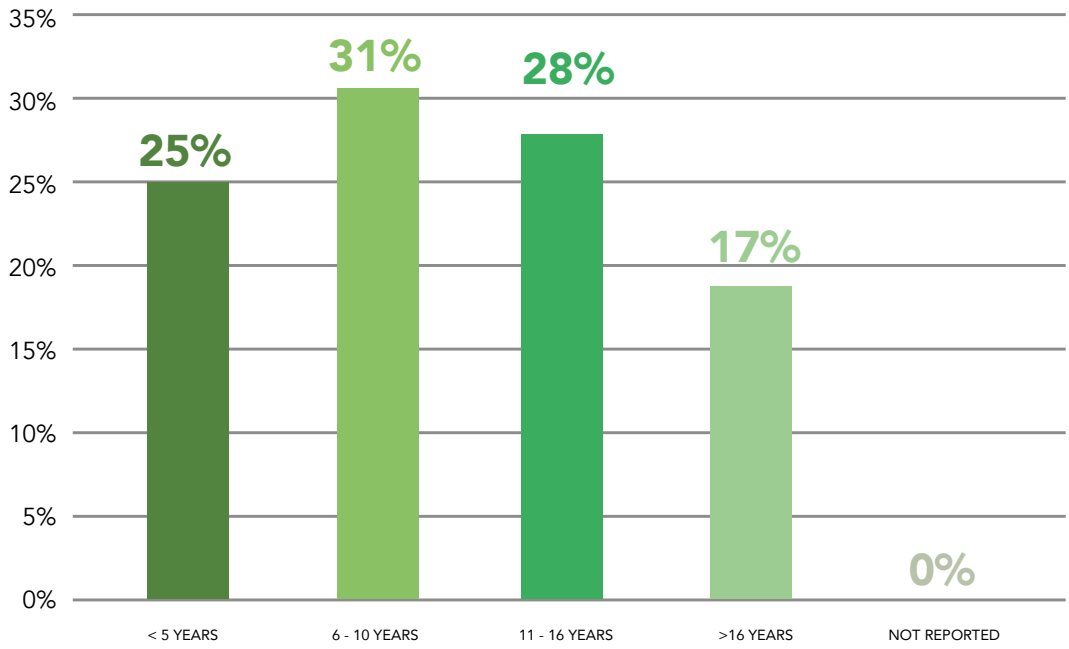
Age range of patients Period Jul-11-2025 to Feb-27-2026



3.4 Seizure Frequency Reduction Across Follow-Up Intervals.

Detailed breakdown of seizure outcomes by follow-up interval (excluding incomplete data):

Result	6 Months Cohort	12 months Cohort	13-24 months Cohort	24-36 months Cohort	>36 months Long-Term Cohort
≥50% Seizure Reduction	18	8	12	21	32
20%–50% Reduction	17	9	10	13	15
<20% Reduction	8	4	10	2	2
Unchanged (Maintained)	4	1	0	7	7
Increased Seizures	2	0	0	0	0
Total patients	**49**	**22**	**32**	**43**	**56**

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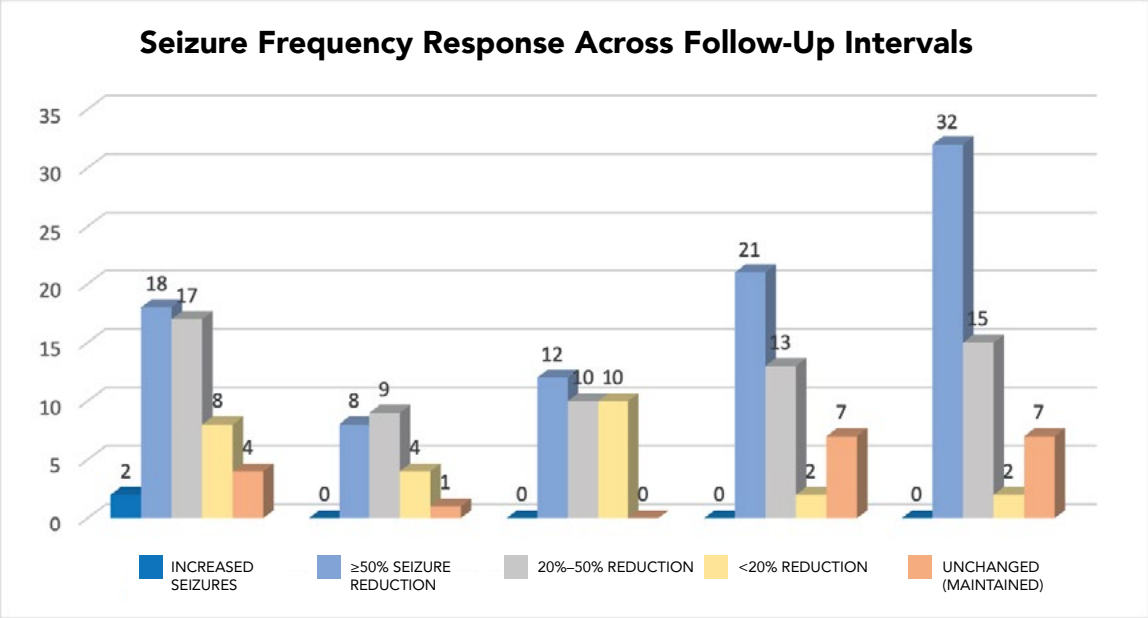

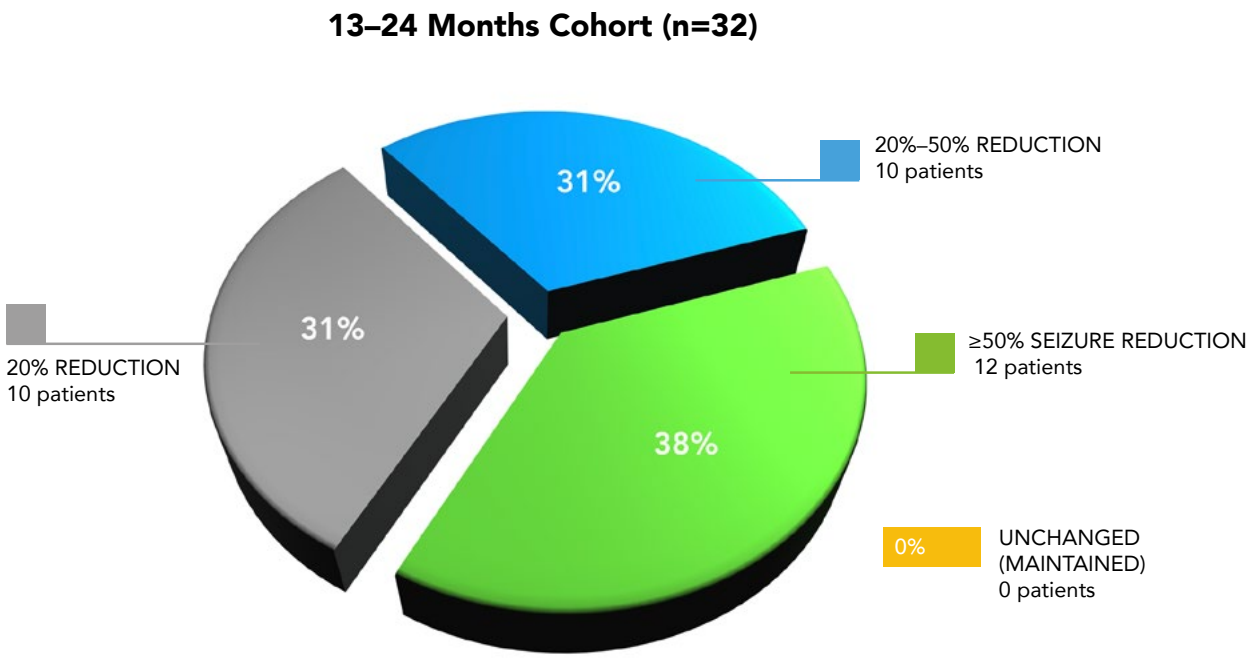

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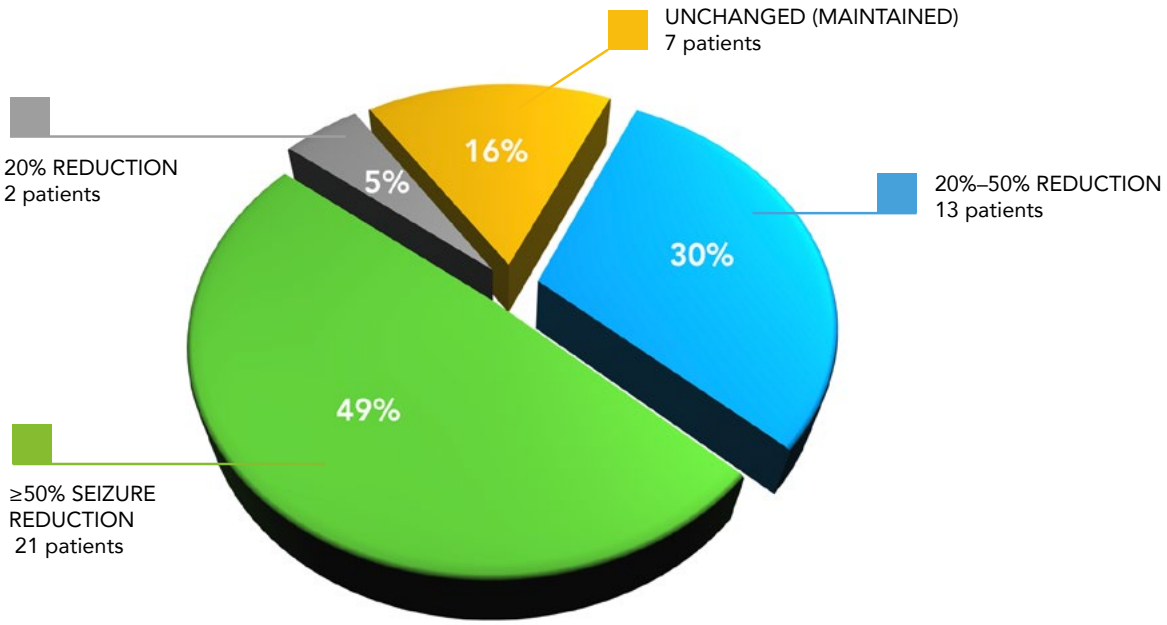
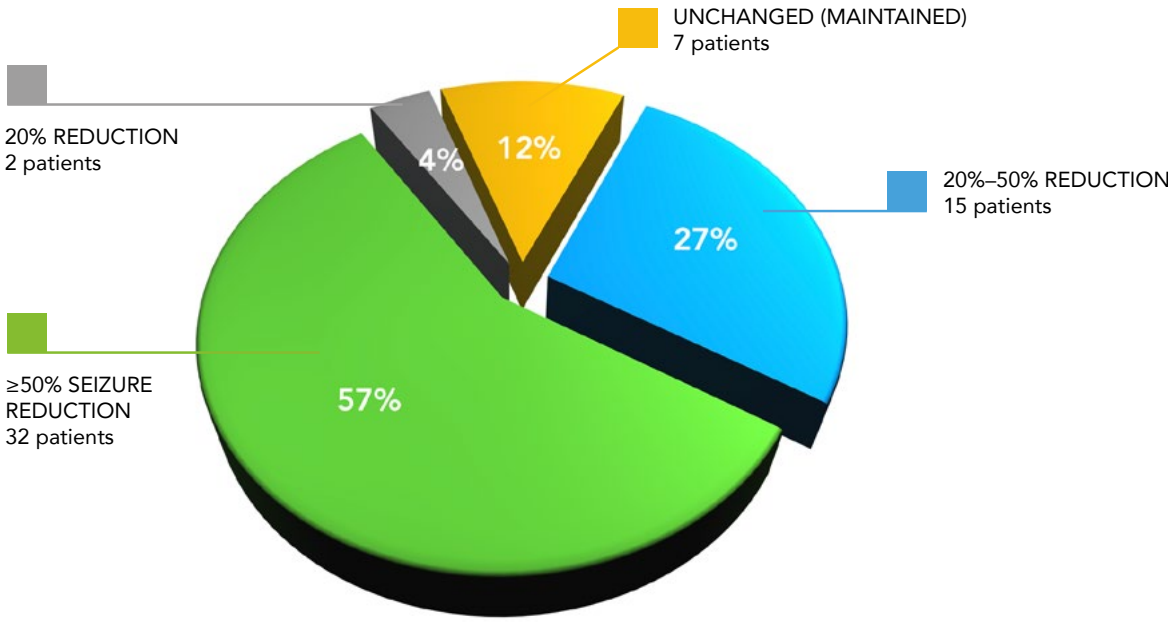
24–36 Months Cohort (n=43)



36 Months Long-Term Cohort (n=56)



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3.5 Adverse Event Reporting & Safety Analysis.

Adverse events recorded during this reporting period (July 11, 2025 – February 27, 2026):

Adverse Event	n	Fatal/Serious Non-Serious
Somnolence	8	Non-Serious
Irritability	2	Non-Serious
Lack of Efficacy	6	Non-Serious
Diarrhea	1	Non-Serious
Sialorrhea / Hypersalivation	1	Non-Serious
Respiratory Failure / Death	1	Serious (Fatal)
Pneumonia / Death	2	Serious (Fatal)
Hyperammonemia	1	Serious
Transaminase Elevation	1	Serious
Total	**24**	

A total of 24 adverse events were reported. Nineteen (19) cases were classified as non-serious. Five (5) cases met criteria for Serious Adverse Events (SAEs), including 3 fatal outcomes resulting from underlying respiratory complications (pneumonia/ respiratory failure).

All safety events were reported to ANMAT in accordance with regulatory timelines and national pharmacovigilance mandates.

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4. CONCLUSIONS & BENEFIT-RISK ASSESSMENT

This 6th Pharmacovigilance Report expands upon previous real-world data, demonstrating sustained therapeutic efficacy and safety in patients with drug-resistant epilepsy. Longitudinal tracking over extended periods (>3 years) provides crucial evidence for a chronic neurological condition where clinical trials are often limited to short durations.

Sustained seizure reduction without evidence of pharmacological tolerance is a landmark finding, as anti-seizure medications frequently exhibit efficacy loss over time.

In long-term extension cohorts (24–36 months and >36 months), overall response rates remained remarkably high: approximately 80% of patients maintained a clinical seizure reduction (with 57% achieving ≥50% reduction at >36 months).

In conclusion, the favorable safety profile and robust benefit-risk ratio solidify Convupidiol® as an essential long-term therapeutic strategy for patients with drug-resistant epilepsy, improving overall quality of life for patients and their families.

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